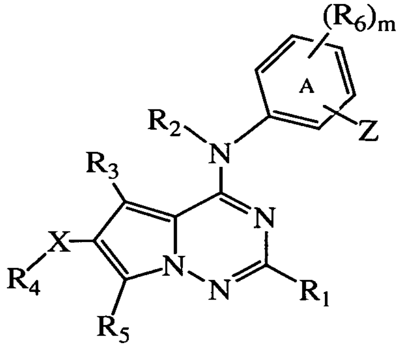
CLAIMS

We claim:

1. A compound having the formula (I)



(I)

its enantiomers, diastereomers, and pharmaceutically-acceptable salts, prodrugs, and solvates thereof, wherein:

X is selected from –O–, –OC(=O)–, –S–, –S(=O)–, –SO$_2$–, –C(=O)–, –CO$_2$–, –NR$_8$–, –NR$_8$C(=O)–, –NR$_8$C(=O)NR$_9$–, –NR$_8$CO$_2$–, –NR$_8$SO$_2$–, –NR$_8$SO$_2$NR$_9$–, –SO$_2$NR$_8$–, –C(=O)NR$_8$–, halogen, nitro, and cyano, or X is absent;

Z is optionally-substituted heteroaryl;

R$_1$ and R$_5$ are independently selected from hydrogen, alkyl, substituted alkyl, –OR$_{14}$, –SR$_{14}$, –OC(=O)R$_{14}$, –CO$_2$R$_{14}$, –C(=O)NR$_{14}$R$_{14a}$, –NR$_{14}$R$_{14a}$, –S(=O)R$_{14}$, –SO$_2$R$_{14}$, –SO$_2$NR$_{14}$R$_{14a}$, –NR$_{14}$SO$_2$NR$_{14a}$R$_{14b}$, –NR$_{14a}$SO$_2$R$_{14}$, –NR$_{14}$C(=O)R$_{14a}$, –NR$_{14}$CO$_2$R$_{14a}$, –NR$_{14}$C(=O)NR$_{14a}$R$_{14b}$, halogen, nitro, and cyano;

R$_2$ is hydrogen or C$_{1-4}$alkyl;

R$_3$ is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano, NH$_2$, or NH(CH$_3$);

R$_4$ is selected from:

(a) hydrogen, provided that R$_4$ is not hydrogen if X is –S(=O)–, –SO$_2$–, –NR$_8$CO$_2$–, or –NR$_8$SO$_2$–;

(b) alkyl, alkenyl, and alkynyl optionally independently substituted with keto and/or one to four R$_{17}$;

(c) aryl and heteroaryl either of which may be optionally independently substituted with one to three R_{16}; and

(d) heterocyclo and cycloalkyl either of which may be optionally independently substituted with keto and/or one to three R_{16}; or

(e) R_4 is absent if X is halogen, nitro, or cyano;

R_6 is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, phenyl, benzyl, aryloxy, and benzyloxy, wherein each R_6 group in turn may be further substituted by one to two R_{18};

R_8, R_9, R_{14}, R_{14a} and R_{14b} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, heterocyclo, and heteroaryl, except when R_{14} is joined to a sulphonyl group as in $-S(=O)R_{14}$, $-SO_2R_{14}$, and $-NR_{14a}SO_2R_{14}$, then R_{14} is not hydrogen;

R_{16} is selected from alkyl, R_{17}, and C_{1-4}alkyl substituted with keto (=O) and/or one to three R_{17};

R_{17} is selected from

(a) halogen, haloalkyl, haloalkoxy, nitro, cyano, $-SR_{23}$, $-OR_{23}$, $-NR_{23}R_{24}$, $-NR_{23}SO_2R_{25}$, $-SO_2R_{25}$, $-SO_2NR_{23}R_{24}$, $-CO_2R_{23}$, $-C(=O)R_{23}$, $-C(=O)NR_{23}R_{24}$, $-OC(=O)R_{23}$, $-OC(=O)NR_{23}R_{24}$, $-NR_{23}C(=O)R_{24}$, $-NR_{23}CO_2R_{24}$;

(b) aryl or heteroaryl either of which may be optionally substituted with one to three R_{26}; or

(c) cycloalkyl or heterocyclo optionally substituted with keto(=O) and/or one to three R_{26};

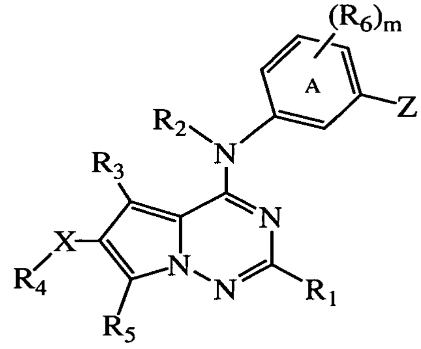
R_{18} and R_{26} are independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, phenyl, five to six membered heterocyclo, (phenyl)C_{1-4}alkyl, phenoxy, and (phenyl)C_{1-4}alkoxy;

R_{23} and R_{24} are each independently selected from hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, aryl, cycloalkyl, heteroaryl, and heterocyclo;

R_{25} is selected from alkyl, substituted alkyl, aryl, heteroaryl, cycloalkyl and heterocyclo; and

m is 0, 1, 2 or 3.

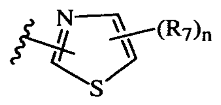
2. A compound of claim 1 having the formula (I*):



(I*),

or a pharmaceutically-acceptable salt, prodrug, or solvate thereof, in which Z is an optionally-substituted, monocyclic five-membered heteroaryl.

3. A compound according to claim 1, or a pharmaceutically-acceptable salt, prodrug, or solvate thereof, in which Z is selected from one of:



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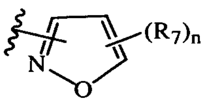

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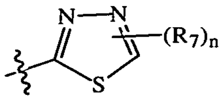

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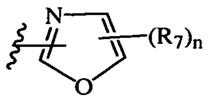

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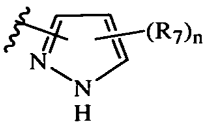

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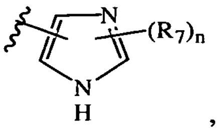

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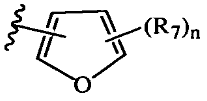

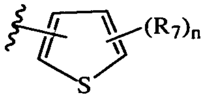

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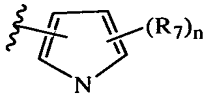

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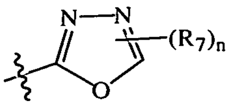
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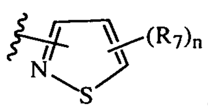
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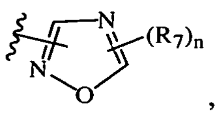
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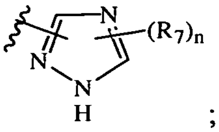
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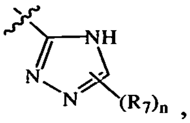
wherein,

n is 0, 1, or 2; and

R_7 is selected from hydrogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, amino, -NH(C_{1-4}alkyl), N(C_{1-4}alkyl)$_2$, hydroxy, C_{1-4}alkoxy, thiol, alkylthio, phenyl, benzyl, phenyloxy, benzyloxy, C_{3-7}cycloalkyl, five-membered heteroaryl, and five to six membered heterocyclo; or as valence permits, R_7 may be taken together with one of two bonds forming a double bond of ring Z to form a keto (=O) group, or two R_7 groups attached to adjacent carbon atoms or an adjacent carbon and nitrogen atom may join to form a fused heterocyclo or carbocyclic ring, said fused ring in turn being optionally substituted with one to two of C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, amino, C_{1-4}alkylalmino, hydroxy, C_{1-4}alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy.

4. A compound according to claim 3, or a pharmaceutically-acceptable salt, prodrug, or solvate thereof, in which Z is one of: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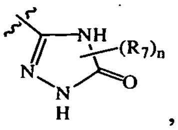
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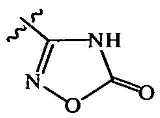

, wherein R_7 is lower alkyl and *n* is 0 or 1.

5. A compound of claim 2, or a pharmaceutically-acceptable salt, prodrug, or solvate thereof, wherein:

Z is a 1,3,4 oxadiazol-2-yl optionally substituted at the 5 position with a group selected from R_{7a}; and

R_{7a} is selected from $C_{1\text{-}4}$alkyl, substituted $C_{1\text{-}4}$alkyl, hydroxy, alkoxy, thiol, alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, amino, -NH($C_{1\text{-}4}$alkyl), and N($C_{1\text{-}4}$alkyl)$_2$.

6. A compound according to claim 2, or a pharmaceutically-acceptable salt, prodrug, or solvate thereof, wherein:

X is selected from –O–, –OC(=O)–, –NR_8C(=O)–, and –C(=O)NR_8–;

R_1 and R_5 are independently selected from hydrogen, alkyl, and substituted alkyl;

R_3 is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano, NH_2, or $NH(CH_3)$;

R_6 is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from $C_{1\text{-}4}$alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, $C_{1\text{-}4}$alkoxy, thiol, $C_{1\text{-}4}$alkylthio, nitro, cyano, carboxy, and carboxy$C_{1\text{-}4}$alkyl; and

m is 0, 1, or 2.

7. A compound according to claim 2, or a pharmaceutically-acceptable salt, prodrug, or solvate thereof, wherein:

R_1, R_2 and R_5 are each hydrogen;

R_3 is methyl, $-CF_3$, or $-OCF_3$;

R_8 and R_9 are selected from hydrogen and $C_{1\text{-}4}$alkyl; and

R_6 is attached to the phenyl ring A at the 4 and/or 6 positions and is selected from $C_{1\text{-}6}$alkyl, trifluoromethoxy, trifluoromethyl, and cyano; and

m is 1 or 2.

8. A compound according to claim 2, or a pharmaceutically-acceptable salt, prodrug, or solvate thereof, wherein:

R_1, R_2 and R_5 are each hydrogen;

R_3 is methyl;

Z is 1,3,4-oxadiazol-2-yl or triazol-5-yl, each of Z optionally substituted with up to one of methyl or ethyl;

X is –C(=O)- or –C(=O)-NH-; when X is –C(=O)-, then R_4 is phenyl or pyridyl optionally substituted with up to two R_{16}; and when X is –C(=O)NH-, R_4 is straight or branched C_{2-6}alkyl or optionally-substituted benzyl;

R_6 is attached to phenyl ring A at the 6 position and is methyl, ethyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, methoxy, ethoxy, or cyano;

R_{16} is selected from C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, NH(C_{1-4}alkyl), N(C_{1-4}alkyl)$_2$ and/or a C_{1-4}alkyl substituted with one to two of halogen, hydroxy, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, NH(C_{1-4}alkyl), and/or N(C_{1-4}alkyl)$_2$; and

m is 1.

9. A compound according to claim 1 or a pharmaceutically acceptable salt, prodrug, or solvate thereof, in which R_1 is hydrogen.

10. A compound according to claim 1, or a pharmaceutically acceptable salt, prodrug, or solvate thereof, in which R_2 is hydrogen.

11. A compound according to claim 1, or a pharmaceutically-acceptable salt, prodrug, or solvate thereof, wherein:

R_3 is methyl, $-CF_3$, or $-OCF_3$.

12. A compound according to claim 1, or a pharmaceutically-acceptable salt, prodrug, or solvate thereof, wherein:

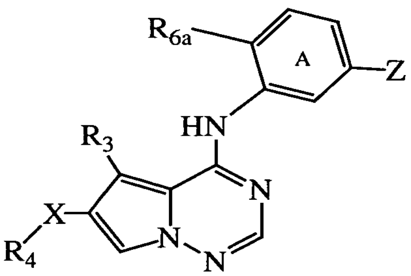
X is –C(=O)– or –C(=O)NH–.

13. A compound according to claim 1, or a pharmaceutically acceptable salt, prodrug, or solvate thereof, in which X is –C(=O)NH– and R_4 is C_{2-6}alkyl, optionally-substituted benzyl, or a heterocyclic or heteroaryl ring selected from diazepinyl, morpholinyl, piperidinyl, and pyrrolidinyl, said heterocycle being optionally substituted with one to two of C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, phenyl, and/or benzyl.

14. A compound according to claim 1, or a pharmaceutically acceptable salt, prodrug or solvate thereof, in which X is –C(=O)– and R_4 is phenyl, pyridyl, pyrimidinyl, or pyrazinyl optionally-substituted with one to two of $C_{1\text{-}4}$alkyl, halogen, hydroxy, $C_{1\text{-}4}$alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, NH($C_{1\text{-}4}$alkyl), N($C_{1\text{-}4}$alkyl)$_2$ and/or a $C_{1\text{-}4}$alkyl substituted with one to two of halogen, hydroxy, $C_{1\text{-}4}$alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, NH($C_{1\text{-}4}$alkyl), and/or N($C_{1\text{-}4}$alkyl)$_2$.

15. A compound according to claim 1 or a pharmaceutically acceptable salt, prodrug, or solvate thereof, in R_5 is hydrogn or CH_3.

16. A compound having the formula,

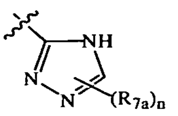


its enantiomers, diastereomers, or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein:

R_3 is methyl or CF_3;

X is –C(=O)– or –C(=O)NH–;

Z is selected from one of



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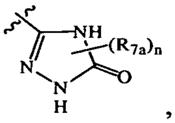

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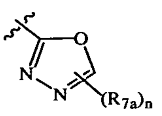

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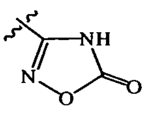

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R_4 is straight or branched $C_{2\text{-}6}$alkyl; cycloalkyl optionally substituted with keto and/or up to two R_{16}; heterocycle or heteroaryl optionally substituted with keto and/or up to two R_{16}; C_{1-4}alkyl substituted with up to three of halogen, trifluoromethyl, cyano, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, phenyl, phenyloxy or benzyloxy, wherein said phenyl group is optionally substituted with one to two R_{16}; or phenyl optionally substituted with zero to two R_{16};

R_{6a} is selected from lower alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4}alkoxy, nitro, amino, C_{1-4}alkylamino, and cyano;

R_{7a} is lower alkyl;

R_{16} is selected from C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$ and/or a C_{1-4}alkyl substituted with one to two of halogen, hydroxy, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, $NH(C_{1-4}alkyl)$, and/or $N(C_{1-4}alkyl)_2$; and

n is 0 or 1.

17. A pharmaceutical composition comprising at least one compound according to claim 1 and a pharmaceutically-acceptable carrier or diluent.

18. A pharmaceutical composition comprising at least one compound according to claim 16 and a pharmaceutically-acceptable carrier or diluent.

19. A method of treating an inflammatory disorder comprising administering to a patient in need of such treatment a pharmaceutical composition according to claim 17.

20. The method of claim 19 in which the inflammatory disorder is selected from asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, diabetes, inflammatory bowel disease, osteoporosis, psoriasis, graft vs. host rejection, atherosclerosis, and arthritis including rhematoid arthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, gouty arthritis, osteoarthritis, pain, and neuropathy.